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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<p>(21) International Application Number: PCT/US92/03125</p> <p>(22) International Filing Date: 16 April 1992 (16.04.92)</p> <p>(30) Priority data: 685,752 16 April 1991 (16.04.91) US</p> <p>(71) Applicant: NATIONAL INSTITUTES OF HEALTH [US/US]; Building 31 Room 2B-62, 9000 Rockville Pike, Bethesda, MD 20892 (US).</p> <p>(72) Inventors: SWEDO, Susan, E. ; 6834 Silver Ann Drive, Lorton, VA 22079 (US). RAPOPORT, Judith, L. ; 3010 44th Place, N.W., Washington, DC 20016 (US). LEONARD, Henrietta, L. ; 5126 Wissioming, Bethesda, MD 20816 (US).</p>		<p>(74) Agents: MURPHY, Gerald, M., Jr. et al.; Birch, Stewart, Kolasch & Birch, 301 North Washington Street, Falls Church, VA 22046-3487 (US).</p> <p>(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), MC (European patent), NL (European patent), SE (European patent).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: METHOD OF TREATING TRICHOTILLOMANIA AND ONYCHOPHAGIA</p> <p>(57) Abstract</p> <p>New methods for using serotonin reuptake inhibitors such as clomipramine, fluvoxamine, fluoxetine and zimelidine are disclosed. The psychiatric diseases to be treated include the impulse control disorders such as trichotillomania, pathological gambling, pyromania, kleptomania, and intermittent explosive disorder. Other conditions such as onychophagia may also be treated with the same medications. Human clinical data for the treatment of trichotillomania (hair-pulling) and onychophagia (nail-biting) are particularly promising.</p>		

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METHOD OF TREATING TRICHOTILLOMANIA AND ONYCHOPHAGIA

This is a continuation in part of Serial Number 207,617 filed April 19, 1988. The contents of that application is incorporated by reference.

FIELD OF THE INVENTION

The invention relates to the treatment of the psychiatric conditions such as trichotillomania and onychophagia pharmacologically. The drugs of choice are serotonin reuptake inhibitors such as clomipramine (ANAFRANIL[®]), fluoxetine (PROZAC[®]), fluvoxamine (FLOXYFROL[®]), zimelidine, sertraline and their salts.

BACKGROUND OF THE INVENTION

Trichotillomania is a common disorder characterized by plucking of hairs from head eyelashes, eyebrows and, less commonly, from other parts of the body. While this behavior may rarely accompany classical obsessive compulsive disorder (OCD) or schizophrenia or depression, the condition is not considered to be part of OCD, schizophrenia or depression and usually is the

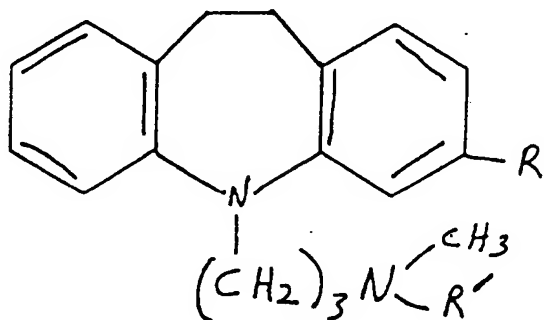
only disorder present. Similarly onychophagia (pathologic nail biting) may occasionally co-exist with these same diseases. However, most nail-biters do not show the obsessive compulsive disorder pattern of behavior, schizophrenia or depression and it is considered an independent entity. The Diagnostic and Statistical Manual of Mental Disorders, (DSM-III) published by the American Psychiatric Association, Washington, 1987, describes compulsions occurring in OCD as "repetitive purposeful, and intentional behaviors that are performed in response to an obsession, according to certain rules or in a stereotyped fashion, while trichotillomania is defined as "recurrent failure to resist impulses to pull out one's hair, resulting in noticeable hair loss." OCD is classified by DSM-III as an anxiety disorder. Trichotillomania is classified by the DSM-III as an impulse control disorder such as kleptomania, pyromania, intermittent explosive disorder and pathological gambling. DSM-III distinguishes between the two separate disorders suggesting a different etiology, natural history, and treatment response. Onychophagia is not listed at all in DSM-III as a mental disorder. When onychophagia and/or trichotillomania are present, self-consciousness about the behavior itself and the resulting disfigurement causes significant distress.

These disorders cause much distress and disfigurement of the individual affected. Accordingly, many techniques have been tried in order to ameliorate the symptoms associated with these

conditions. Several methods of treating hair-pulling and nail-biting have been tried heretofore including psychotherapy, behavior modification, hypnosis, relaxation therapy, and administration of varied pharmaceutical preparations. Beauticians have provided skin, hair, and nail treatments at high cost to patients. While some of these approaches have proven efficacious in specific populations, no treatment has proven effective in treating a wide range of patients wherein the common problem pattern is trichotillomania or onychophagia.

Serotonin reuptake inhibitors are chemicals whose primary mechanism of action is blocking the reuptake of serotonin as opposed to blocking the uptake of noradrenaline or dopamine.

The 5-(3-dimethylaminopropyl)-10, 11-dehydro-5H-dibenzazepines of the formula



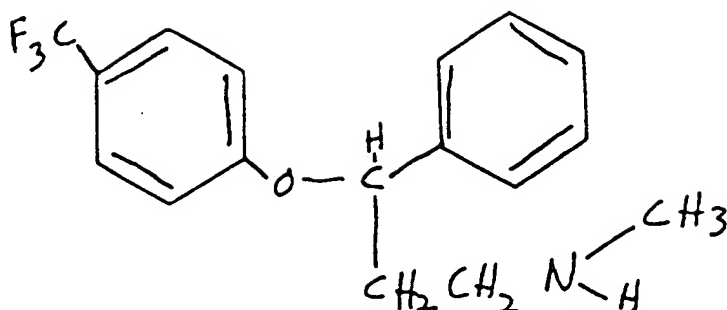
wherein $R = H$ or Cl and $R' = H$ or CH_3 have long been used as antidepressants. If R and R' are both H , then the compound is desipramine, an anti-depressant compound which lacks the claimed usefulness. Desipramine has been reported (Benfield et al, Drugs 32, p. 313-334 at 317 (1986)) to require over fifteen times the

concentration of clomipramine for the same serotonin reuptake inhibitory effect. Yaryura-Tobias et al, (Current Therapeutic Research, VOL. 20 (4) p. 541-8 (1976)) described the use of clomipramine (see above where $R = Cl$, $R' = CH_3$) for treatment of classical obsessive compulsive neurosis. In 1985, Krishnan et al published a review in which the use of chlorpromazine, an antipsychotic drug, was suggested for use in treatment of trichotillomania if the hair-pulling resulted from schizophrenia or OCD. There has been no indication this drug should be used in the treatment of trichotillomania when unrelated to the other disorders.

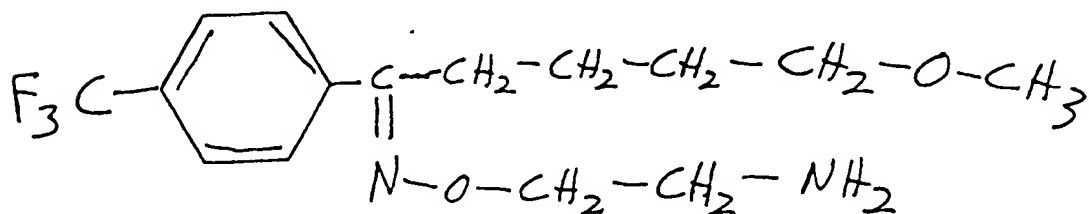
Finally, the use of Clomipramine in obsessive compulsive patients was believed by many authorities to be of value in treating OCD but only in patients having OCD accompanied by depression. For example, Marks and his associates stated, "when depression is minimal, clomipramine has no demonstratable value. ...Clomipramine effects mood more than rituals." (Brit. J. Psychiat. (1980) 136, p. 1-25 at 22). Others have found clomipramine's anti-obsessional effects to be independent of its antidepressant activity.

Fluoxetine hydrochloride {(±)-N-methyl-3-phenyl-3-[(α,α,α -trifluoro-p-tolyl)-oxy]-propylamine hydrochloride} is a known antidepressant which is known to inhibit the reuptake of serotonin. Its chemical formula is:

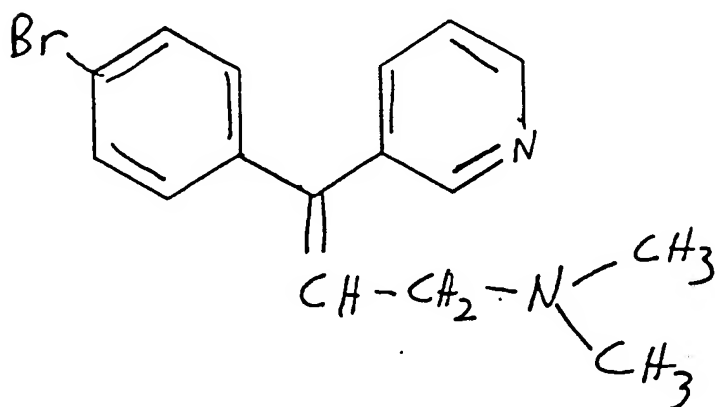
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Fluvoxamine malate [5-methoxy-4'-(trifluoromethyl) valerophenone-(E)-O-(2-aminoethyl)oxime maleate (1:1)] is a known antidepressant compound which is known to inhibit serotonin reuptake. Its chemical formula is:



Zimelidine is another known inhibitor of serotonin reuptake and its chemical formula is:



SUMMARY OF THE INVENTION

It has now been discovered that serotonin reuptake inhibitors such as clomipramine, fluoxetine, fluvoxamine, zimelidine and sertraline are effective in treating other psychiatric disorders such as impulse control disorders such as trichotillomania and also the disorder onychophagia.

One aspect of the invention is the use of these types of compounds to treat a number of psychological and psychiatric conditions which were previously not known to be treated adequately by any chemical means. These conditions include impulse disorders such as trichotillomania, pathological gambling, kleptomania, pyromania and other recognized impulse control disorders. Other conditions not previously recognized as specific psychiatric conditions such as onychophagia may also be treated using serotonin reuptake inhibitors. Especially preferred conditions to treat with serotonin reuptake inhibitors are trichotillomania, onychophagia and other pathological conditions involved with "excess personal grooming" behavior. Such conditions include repetitive or compulsive picking at the skin, (especially face picking), preening, licking or examining skin or other parts of the body regardless of whether or not they are classified as impulse control disorders.

Currently, the only serotonin reuptake inhibitors known well enough to give to a human are clomipramine, fluvoxamine and

fluoxetine. It is contemplated that other serotonin reuptake inhibitors especially those previously tried in humans such as zimelidine and sertraline will also be effective for the same purposes in pharmacologically acceptable concentrations.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Some of applicants work relating to this invention has been published in Swedo et al, New England Journal of Medicine, Vol. 321 p. 497-501 (1989), the contents of which are incorporated by reference. Other published work includes Leonard et al, Archives General Psychiatry (1991), the contents of which are incorporated by reference. Both publications describe the patient screening and experimental details.

Since the work of applicants, some psychiatrists are considering classifying trichotillomania and possibly onychophagia as obsessive compulsive disorders because they respond to medications effective to treat OCD. For example, Winchel et al, Benarroche and Stanley et al, Am. Psych. Assn. 143rd Ann. Meet. NY May 12-17, 1990 Abstracts # NR295, NR327 and NR292 respectively. As of now, this classification is not completely accepted. Onychophagia is still not recognized as a psychiatric disorder but for the purposes of this patent application it may be so included. Other psychiatric conditions within the same class of disorders as trichotillomania, currently

known as impulse control disorders, may also be treated with serotonin reuptake inhibitors as well.

Serotonin reuptake inhibitors may be administered in any pharmaceutically acceptable carrier and may be of any pharmaceutically acceptable salt. The hydrochloride salt is particularly preferred for clomipramine and fluoxetine whereas the maleate is particularly preferred for fluvoxamine. Combinations of one or more additional medications with the serotonin reuptake inhibitor contemplated may be used as indicated, including combinations including plural serotonin reuptake inhibitors.

The preferred dosage for clomipramine is about 10 to about 300 mg/day. The preferred dosage for fluoxetine is about 5 to about 80 mg/day. The preferred dosage for fluvoxamine is about 10 to about 300 mg/day. The preferred dosage for zimelidine and sertraline is about 10 to about 300 mg/day. The dosage may be administered daily or may be divided for administration 2-6 times per day. Dosages given less often than daily may also be used.

Also included within the scope of this invention are the pharmaceutically acceptable salts, esters, salts of such esters, nitrile oxides, or any other covalent linked or non-linked compounds which upon administration to the cells or individual, is capable of providing (directly or indirectly) the compounds of the invention or a biologically active metabolite thereof. All of these compounds are active and relatively non-toxic at

concentrations sufficient for effective inhibition of the symptoms of trichotillomania and onychophagia.

It is possible for the compounds of the present invention to be administered alone in solution. However, in the preferred embodiment, the active ingredient(s) may be used or administered in a pharmaceutical formulation. These formulations comprise at least one active ingredient, together with one or more pharmaceutically acceptable carriers and possibly other active or inactive therapeutic ingredients. As included within the scope of the invention, "acceptable" is defined as being compatible with other ingredients of the formulation and relatively non-injurious to the patient or host cell. These carriers include those well known to practitioners in the art as suitable for oral, rectal, nasal, topical, buccal, sublingual, vaginal, transdermal, subcutaneous, intradermal, intramuscular, intravenous or other parenteral administration. Specific carriers suitable for use in the invention are further defined below.

While the preferred route of administration is oral and in some situations parental, other route of administration may have additional benefits for patients not wishing to receive medication in a conventional manner for what may not be perceived as a medical condition. Further, other forms of administration, particularly topical provide more patient involvement and thus also may increase patient compliance.

Formulations of the present invention suitable for oral administration include sustained release formulations and may be presented in discrete units such as capsules, cachets, spansules or tablets each containing a predetermined amount of the active ingredient(s). The shape and form of the solid are immaterial and it may be composed of smaller solids such as powders or granules. The formulation may be in liquid form such as a solution, suspension, oil-in-water or water-in-oil emulsion. Other acceptable formulations include a bolus, electuary or paste. Spansules of slow release in the gastrointestinal tract are particularly preferred.

The oral dose may optionally be provided with an enteric coating to provide release in any part of the digestive track so desired.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient with an acceptable flavorant such as sucrose and acacia or tragacanth; with an inert ingredient(s) such as gelatin or glycerin; or a combination of both. Mouthwash comprising the active ingredient and a liquid carrier are also acceptable in accordance with the invention.

Formulations for topical and transdermal administration include a suitable carrier such as a cream or base of other material to facilitate contact with the skin or mucus membranes. The active ingredient(s) contained therein may be charged, or

converted into a salt in order to permit crossing the surface under the influence of an electrical field. Alternatively, the active ingredient may be derivatized in order to enhance absorption or transport across the cell layer.

Formulations for rectal administration may be presented as a suppository with a suitable base, for example, comprising cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulas containing such carriers as are known in the art to be appropriate in addition to the active ingredient(s).

Formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic and isosmotic sterile injection solutions which may contain antioxidants, buffers, bacteriostats, and solutes which render the formulation isotonic with the body fluids of the intended recipient and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose sealed containers, such as ampules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier (e.g. water, saline) for injection immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from powders, granules and tablets of the kind

previously described. In all cases, the final product is preferably free of pyrogens.

For long term therapy, oral administration is highly desirable. Depending on the chemical structure of particular serotonin reuptake inhibitor it may be necessary to buffer or otherwise protect the composition in the neutral range to provide adequate bioavailability.

EXAMPLE

13 trichotillomania patients and 14 onychophagia patients completed the studies which evaluated the effectiveness of a serotonin reuptake blocking drug in comparison with the standard tricyclic antidepressant desipramine. None had a current diagnosis of primary affective disorder so that the effects could not be attributed to an anti-depressant effect. All had been on at least one form of unsuccessful treatment previously. Unsuccessful treatments included: behavioral modification, relaxation, psychotherapy, inpatient therapy, aversion therapy, hypnosis, biofeedback, aversion reinforcement, gift incentives, a variety of cosmetic treatments and pharmacological treatments with nortriptyline, amitriptyline, prazepam, alprazolam, imipramine, chlordiazepoxide and trazodone. Many patients had attempted more than one treatment but no significant relief was provided by any of these treatments. Other treatments have been

proposed in the past with none being effective for more than a short-term.

For both studies, double blind experiments were performed for ten weeks of active medication for trichotillomania and onychophagia where clomipramine and desipramine were used in a cross over trials of five weeks each. Significant improvement was noted with the use of clomipramine but not desipramine.

While both of these drugs are known antidepressants and are structurally very similar as noted in the Background of the Invention, only clomipramine inhibits serotonin reuptake. As shown in the data below, only clomipramine was effective at treating trichotillomania and/or onychophagia.

Fluoxetine was also given to two trichotillomania patients after the double blinded study was complete and showed a similarly positive therapeutic response to this drug as well. The base-line impairment scores were 6 and 7 and after six months the scores were 2 and 3 respectively.

Fluoxetine was also given to six individuals with onychophagia who had reported a positive response to clomipramine but disliked the side effects. This was an open trial for 4.4 to 3.8 months. Two individuals continued on fluoxetine for six and eight months respectively and reported a 50% improvement. The remainder of the subjects did not feel their improvement was sufficient to warrant the expense or unpleasantness of continued drug treatment.

All references mentioned above and the parent patent application are hereby incorporated by reference into this application in their entirety.

The foregoing description of the specific embodiments will so fully reveal the general nature of the invention that others can, by applying current knowledge, readily modify and/or adapt for various applications such specific embodiments without departing from the generic concept, and, therefore, such adaptations and modifications should and are intended to be comprehended within the meaning and range of equivalents of the disclosed embodiments. It is to be understood that the phraseology or terminology employed herein is for the purpose of description and not of limitation.

CLINICAL RATINGS DURING CLONIPRAMINE AND DESIPRAMINE TREATMENT OF 13 WOMEN WITH TRICHOTILLOMANIA

SCALE	BASE LINE	mean \pm SD		CLONIPRAMINE	CLONIPRAMINE vs. DESIPRAMINE	t	P value
		PLACEBO	DESIPRAMINE				
Severity of symptoms	15.9 \pm 3.8	14.4 \pm 4.6	14.4 \pm 3.9	10.6 \pm 6.4		1.71	0.11
Trichotillomania impairment	6.8 \pm 1.7	6.6 \pm 1.0	6.2 \pm 1.7	4.2 \pm 2.7		2.47	0.03
Clinical progress	10.0 \pm 0.0	9.7 \pm 1.0	8.7 \pm 2.4	4.7 \pm 3.1		3.35	0.006
Anxiety	3.7 \pm 1.8	2.9 \pm 0.7	2.7 \pm 1.4	1.8 \pm 1.1		2.14	0.05
Depression	2.7 \pm 1.6	2.4 \pm 0.8	2.2 \pm 1.4	1.5 \pm 0.9		2.99	0.01

All comparisons between the drugs were made by two-tailed, paired t-test. The ratings shown are those made after five weeks of treatment with each of the two drugs.

CLINICAL RATINGS DURING CLONIPRAMINE AND DESIPRAMINE TREATMENT OF SEVERE MAILBITING

MEASURE	BASE LINE	PLACEBO	mean \pm SD		F	P value
			DESIPRAMINE	CLONIPRAMINE		
Mail Severity	17.1 \pm 3.3	15.0 \pm 3.7	15.3 \pm 5.6	12.6 \pm 5.6	3.75	0.04
Mailbiting Impairment	7.6 \pm 0.6	7.6 \pm 0.7	7.2 \pm 1.1	6.4 \pm 2.1	5.27	0.02
Mail Clinical Progress	10.0 \pm 0.0	8.9 \pm 1.2	9.0 \pm 2.4	7.1 \pm 3.0	7.65	0.01
NIMH Global Anxiety	2.8 \pm 1.0	3.2 \pm 1.9	2.3 \pm 1.4	2.4 \pm 1.2	0.04	NS
NIMH Global Depression	1.7 \pm 1.1	1.6 \pm 1.2	1.6 \pm 0.9	1.5 \pm 0.8	0.18	NS

All comparisons between the drugs were made by repeated measures ANOVA. The ratings shown were made after five weeks of treatment with each of the two drugs. P values reported are one-tailed for the Mail Scales and are two-tailed for anxiety and depression scales.

* NIMH indicates National Institute of Mental Health and NS indicates not significant.

We Claim:

1. A method for preventing or treating an impulse control disorder in a patient comprising administering an effective amount of a serotonin reuptake inhibitor.

2. The method of claim 1 wherein the serotonin reuptake inhibitor is selected from the group consisting of clomipramine, fluoxetine, fluvoxamine, zimelidine, sertraline and salts thereof.

3. The method of claim 2 wherein clomipramine hydrochloride, fluoxetine hydrochloride or fluvoxamine maleate is used.

4. The method of claim 3 wherein the dosages of clomipramine hydrochloride, fluoxetine hydrochloride or fluvoxamine maleate are about 10 to about 300 mg/day, about 5 to about 80 mg/day and about 10 to about 300 mg/day respectively.

5. The method of claim 1 wherein said inhibitor is administered orally.

6. The method of claim 1 wherein said impulse control disorder is selected from the group consisting of kleptomania, pyromania, trichotillomania, pathological gambling and intermittent explosive disorder.

7. The method of claim 1 wherein said impulse control disorder involves excess personal grooming.

8. The method of claim 1 wherein the patient's impulse control disorder does not accompany depression, schizophrenia or obsessive compulsive disorder.

9. A method for preventing or treating trichotillomania or onychophagia comprising administering an effective amount of a serotonin reuptake inhibitor.

10. The method of claim 9 wherein said serotonin reuptake inhibitor is selected from the group consisting of clomipramine, fluoxetine, fluvoxamine, zimelidine, sertraline and salts thereof.

11. The method of claim 10 wherein clomipramine hydrochloride, fluoxetine hydrochloride or fluvoxamine maleate is used.

12. The method of claim 11 wherein the dosages of clomipramine hydrochloride, fluoxetine hydrochloride or fluvoxamine maleate are about 10 to about 300 mg/day, about 5 to about 80 mg/day and about 10 to about 300 mg/day respectively.

13. The method of claim 9 wherein said serotonin reuptake inhibitor is administered orally.

14. The method of claim 9 wherein the patient's trichotillomania or onychophagia does not accompany depression, schizophrenia or obsessive compulsive disorder.

15. The method of claim 9 wherein the disorder involves excess personal grooming.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/03125

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A01N 43/62

US CL :514/219

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/217

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

MEDLINE, CAS, APS; SEARCH TERMS CHEMICAL STRUCTURE TRICHOTILLOMANIA; ONYCHOPHAGIA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	THE JOURNAL OF NERVOUS AND MENTAL DISEASE VOLUME 168, NO. 8, ISSUED 1980, S. SNYDER, "TRICHOTILLOMANIA TREATED WITH AMITRIPTYLINE", PAGES 505-507 SEE ESPECIALLY PAGE 506, SECOND COLUMN	<u>1-3,9,13</u> 4-8, 10-12, 14,15
X Y	PSYCHIATRY VOL. 26, NO.2. ISSUED 1985, K.R.R. KRISHNAN ET AL., "TRICHOTILLOMANIA A REVIEW", PAGES 123-128, ESPECIALLY BOTTOM PAGES 126 BRIDGING TO TOP PAGE 127.	<u>1-6,9-11,13</u> 7,8,12,14-15
Y, P	J. CLINICAL PSYCHIATRY, VOL. 52, NO.2, ISSUED FEBRARY 1991 M.A. STANLEY ET AL "TREATMENT OF TRICHOFILLOMANIA WITH FLOUXETINE " SEE PAGE 252	1-15
Y	J. CLINICAL PSYCHIATRY, VOL. 52, NO. 6, ISSUED JUNE 1991, ALEXANDER "FLUOXETINE TREATMENT OF TRICHOFILLOMANIA", SEE PAGE 88	1-15
Y,P	US,A 5,008,262 (SWEDO) 16 APRIL 1992, SEE ENTIRE DOCUMENT	1-15



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be part of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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